44.001

Secondary bacterial infections - The other side of influenza pathogenesis

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Secondary bacterial infections are a major cause of morbidity and mortality following influenza. This was especially true during past pandemics, where 50-95% of all deaths were complicated by or attributed to bacterial pathogens. The emergence in 2009 of a new pandemic strain has increased the urgency for us to understand how bacteria work together with influenza viruses to cause pneumonia. Several mechanisms have been postulated to explain this interaction. The viral neuraminidase has been shown to enhance adherence of bacteria and increase the incidence of bacterial pneumonia. The lack of glycosylation of the surface proteins of viruses emerging from the avian reservoir contributes to both primary virulence and secondary bacterial infections by preventing viral clearance. Recent work has implicated the influenza A virus protein PB1-F2 as a virulence factor which enhances secondary bacterial pneumonia. Although the novel H1N1 swine-origin influenza virus has molecular signatures that predict viral virulence in humans including high neuraminidase activity and low glycosyltation, it does not possess a functional PB1-F2 protein. In the context of a pandemic, it is likely that secondary bacterial complications and overall mortality will be lower because of this absence. However, reassortment or mutation to restore PB1-F2 function to this virus could herald greatly expanded virulence.

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44.002

The role of mucosal antiviral immunity in bacterial secondary lung infections

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Bacterial co-infections are typically a major cause of mortality following influenza infection, including infection with the pandemic H1N1 Cal/04/09 virus, but the reason for this increased susceptibility is only poorly understood. We have found that alveolar macrophages are the first line of defense against pulmonary pneumococcal and MRSA infection, and can very rapidly (within 4 hr) clear almost all bacteria after *in vivo* challenge with a relatively low dose (up to 105 CFU of pneumococci). However, prior influenza virus infection inhibits this clearance mechanism and causes normally sublethal doses of bacteria to be 100% lethal. This is due to production of interferon (IFN)-gamma during pulmonary T cell responses to influenza infection, which inhibits scavenger receptor expression by alveolar macrophages and in turn, leads to decreased bacterial clearance from the lung. Thus, the increased anti-viral immune response causes decreased protection against pulmonary bacterial infection. These results and the potential of vaccine and H1N1 influenza infection.

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44.003

Alteration of the Innate Immune Rheostat and Susceptibility to Secondary Bacterial Superinfections

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Infection of mucosal surfaces culminates in long term modifications that impact on future inflammatory events. These modifications do not necessarily depend on persistence of the original pathogen but on the altered microenvironment which occurs upon resolution. This ''imprinting'' by the first pathogen involves subtle alterations of epithelial cells, resident mucosal macrophages, production of mediators that recruit immune cells and importantly, an alteration in the local microbial commensal community.

Bacterial super-infections are common following influenza and lead to a worse prognosis often resulting in death. Analysis of post-mortem specimens from the 1918-19 pandemic shows a bacterial prevalence greater than 95%. Control of initial bacterial growth relies on multiple components of innate immunity, many of which are disrupted following influenza virus infection in murine models. One key determinant that limits bacterial growth is the responsiveness of airway macrophages to bacteria in the airspaces. We show that influenza virus limits responsiveness by enhancing an innate immune negative regulator (CD200 receptor) during resolution of adaptive immunity. Removal of this single receptor limits bacterial burden in the airway and lung and completely prevents peripheral dissemination, sepsis and mortality. Adjustment of innate reactivity may therefore provide a novel opportunity to prevent life-threatening consequences of lung influenza virus infection.

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44.004

Lessons from 1918 and the current H1N1 pandemic on the role of bacterial infections during pandemic influenza

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The current pandemic of H1N1 influenza has features reminiscent of 1918 including infections and excess morbidity in young adults. The impact in terms of mortality has however been far less severe. This is in part due to lesser virulence of the virus, but also to the introduction of antibiotics and most recently to the introduction of conjugate pneumococcal vaccines in some countries that have reduced the morbidity of influenza associated pneumonia. During the 1918 pandemic, post mortem data suggest that the majority of deaths were associated with bacterial superinfection leading to pneumonia following 4 - 6 days after influenza. A